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NanOx-based multiscale modeling of the biological dose in BNCT to estimate the impact of boron microdistributions

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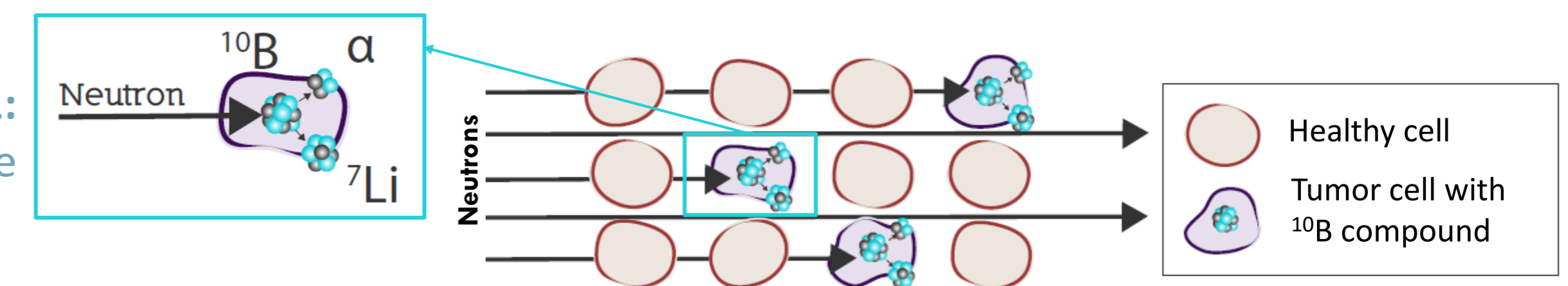
1. BNCT

Boron Neutron Capture Therapy (BNCT): a compound enriched in **boron-10 (¹⁰B)** isotope is selectively accumulated inside tumor cells and the patient is subsequently **irradiated with neutrons**.

- Thermalized neutrons captured by the ¹⁰B → **emission of alpha particles and lithium ions** of very high linear energy transfer (LET) and short range (< 9 μm).
- Exclusively damage the cells containing ¹⁰B and not the neighboring ones.
- BNCT gained importance in recent years thanks to the **new generation of accelerators** [1].

Dual radiotherapy (targeting + external irradiation), selective at cell level

Figure 1: BNCT principle



2. Context and Objectives

The combined external neutron irradiation and local damage caused by the high-LET ions complexify BNCT dosimetry and involves **different biological contributions from tissue to DNA scales**. Approximations have been done for years, but improvements in **computing systems and biophysical models** allow to introduce **more detailed calculations**.

Main objectives:

- Quantify the impact of ¹⁰B **microdistribution** using multiscale modeling
- **Improve biological dose calculation precision**, with the **NanOx** biophysical model, by considering **each secondary particle at all energy steps**.
- Obtain **cell survival** and **Tumor Control Probability (TCP)** for BNCT treatment cases

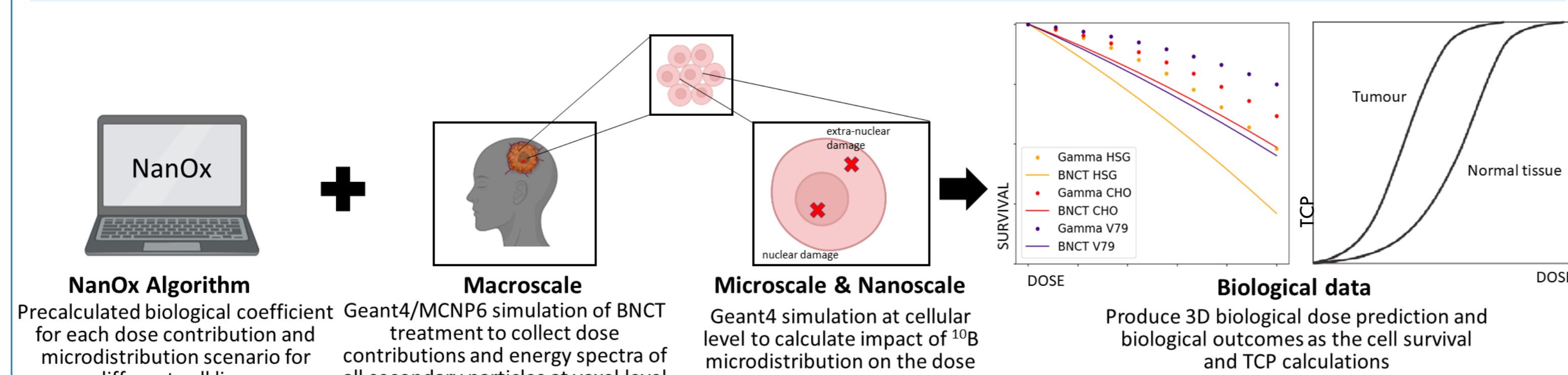


Figure 2: Multiscale methodology planned by the end of the project

4. Material and Methods

Biophysical multiscale methodology:

- Main contributors to dose in BNCT: **photons (D_γ)**, **protons (D_H)** and **¹⁰B (D_B)** (He and Li ions)
- According to the LQ model, cell survival in mixed fields is given by: $S_{mix} = e^{-\alpha_{mix}D_{mix} - \beta_{mix}D_{mix}^2}$
- From the NanOx model: $\alpha_{mix}D_{mix} = \tilde{\alpha}_H D_H + \tilde{\alpha}_B D_B + \alpha_\gamma D_\gamma$
- $\sqrt{\beta_{mix}}$ computed the same way as the α_{mix} replacing by $\sqrt{\beta_{mix}}$ in equation (in line with [4]).

$$\text{MACRO: } \tilde{\alpha}_H = \int_H spect. f_H(E) \frac{1}{E} \frac{dE}{m_v} \int_0^E \alpha_H(E') dE'$$

$$\text{MICRO: } \tilde{\alpha}_B = \frac{1 - \bar{S}_1}{\bar{d}_1}$$

$f_H(E_0) = \frac{1}{D_H} \left(\frac{\partial D_H}{\partial E_0} \right)$, $\alpha_H(E')$: coefficient for mono-energetic ions, E : initial energy.

\bar{d}_1 : mean dose deposited during boron fragmentation in a multi-cellular volume. \bar{S}_1 : mean cell survival for a single boron fragmentation.

Registration at voxel level of all secondary particle **dose deposition** and their **kinetic energy**. Includes an integration from ion emission to stop.

Calculation of $\tilde{\alpha}_B$ and $\tilde{\beta}_B$ coefficients as a **function of the ¹⁰B microdistribution** through NanOx. Also consider an integration of α coefficients over all ion energy steps

In the preliminary results presented, **the cell nucleus was the only sensitive volume considered**

3. NanOx algorithm

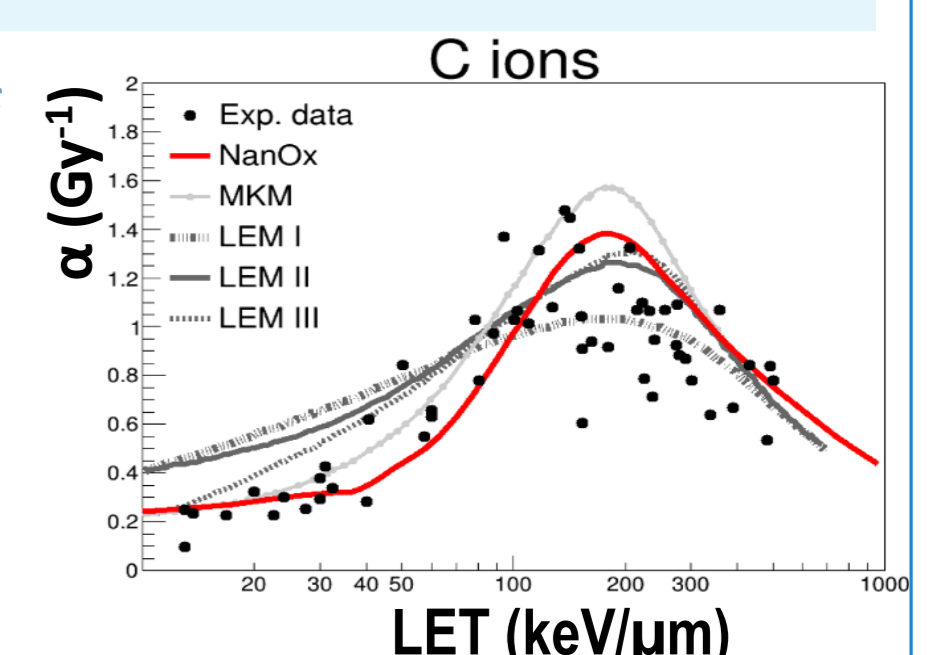
NanOxTM: **Nanodosimetry and Oxidative stress** [2]

Predict cell survival, with associated biological α and β parameters. It combines:

- 1) **Local lethal events** due to particle tracks in **nanometric targets**
- 2) **global events**: modeling of **sublethal lesion accumulation** and **oxidative stress** (reactive chemical species) in micrometric sensitive volume

- Originally **developed to predict RBE** in the context of hadrontherapy: validated for HSG, V79 and CHO-K1 cell lines [3].
- Currently **being adapted for BNCT** ion energies and consideration of **extra-nuclear damage**.

Figure 3: Comparison of experimental α values of V79 cells for carbon ions with different biophysical models and NanOx[3]



5. Preliminary results

MACROSCALE: Comparison of the present multi-scale approach with the current way of BNCT effect estimation (simplified study)

Geant 4. Snyder head phantom with various cerebral tumor depths loaded with 20ppm ¹⁰B, irradiated with 10 keV neutrons. Homogeneous ¹⁰B-microdistribution assumed.

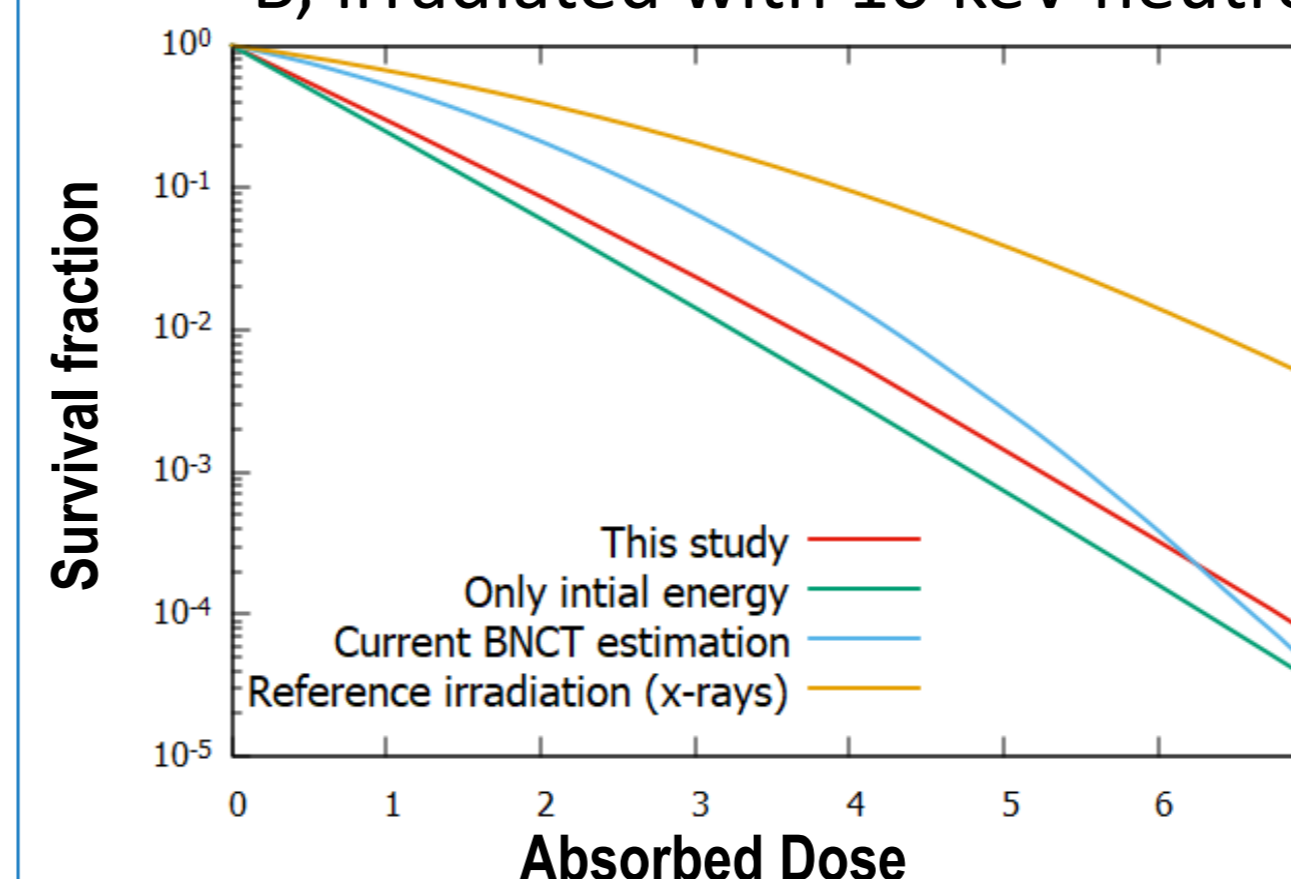


Figure 4:

Survival curves obtained for HSG cells & 2cm depth for: **this study, using NanOx model and secondary particle effect at all the energy steps**; compared with: **this study, but only taking into account the α of the initial energy**; the current way of BNCT effect estimation (known as the weighted dose [5]); and **the reference photon curve**.

MICROSCALE: Impact of ¹⁰B microdistributions (simplified study)

Geant4. Multicellular geometry with different ¹⁰B microdistributions considering only He and Li ions. **TCP calculated as:**
 $TCP = e^{-N_0 * S(D)}$

With N_0 the number of tumor cells and S the mean cell survival in the spheroid receiving a dose D

Large influence of microdistribution. The "nucleus" one is the most efficient

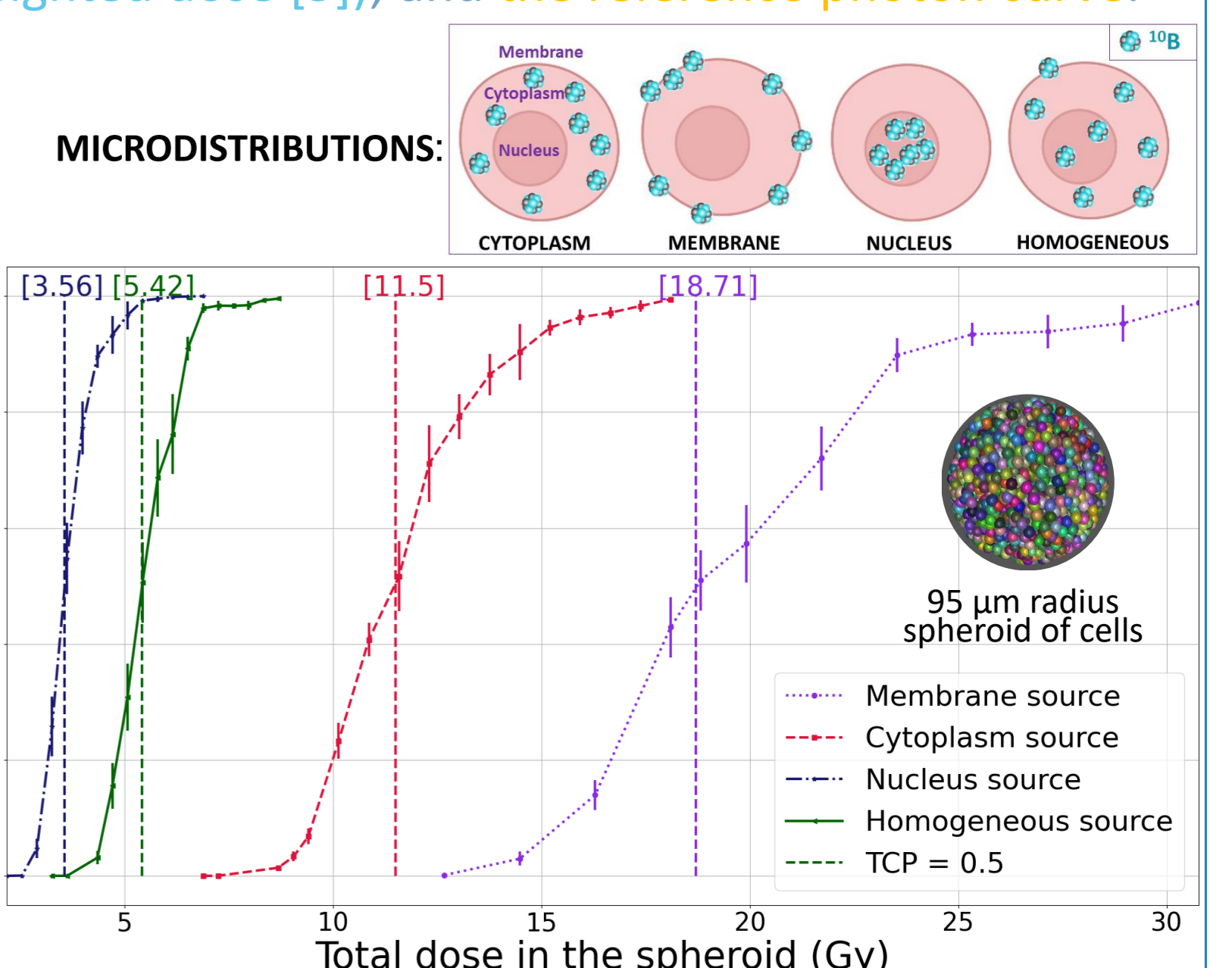


Figure 5: Result of TCP calculation for CHO-K1 cells with the distributions described above. The written values correspond to TCP = 0.5

6. Conclusions and perspectives

Conclusions:

- The proposed **new multiscale approach** aims at taking into account the effect of **each secondary particle at all energy steps down to 0**, depending on the **intracellular ¹⁰B microdistribution**, up to the prediction of **cell survival or TCP**.
- Preliminary results in simplified macroscopic study case showed **differences with current BNCT formalisms**, which may suggest the necessity of this exhaustive energy step procedure.
- Results in **¹⁰B microdistribution** suggest the **importance of considering this approach** when calculating the biological dose in BNCT.

Perspectives:

- **Microscopic calculation improvements:** further detailed studies are in progress to finish quantifying the impact of all ¹⁰B distributions, including evaluation of realistic cell geometry impact and extra-nuclear damage contributions.
- **Link microscopic and macroscopic calculations:** apply the dependency of ¹⁰B microdistribution inside the α_i, β_i parameters described in the macroscopic mixed field calculation. Plus evaluate the synergy damage of protons, gamma, He and Li ions.
- **Experiments for radiobiological data:** irradiations with low-energy protons, He and Li ions are planned at ALTO facility (Orsay, France) in next years to refine NanOx calculations at low energy and validate cancerous cell lines [6]
- **Comparison with experimental data:** model will be validated against BNCT *in vitro* experiments from literature, such as those performed at JRR-4 reactor [7] and at ILL [8]. The model will eventually be applied to real patient data from BNCT irradiations.

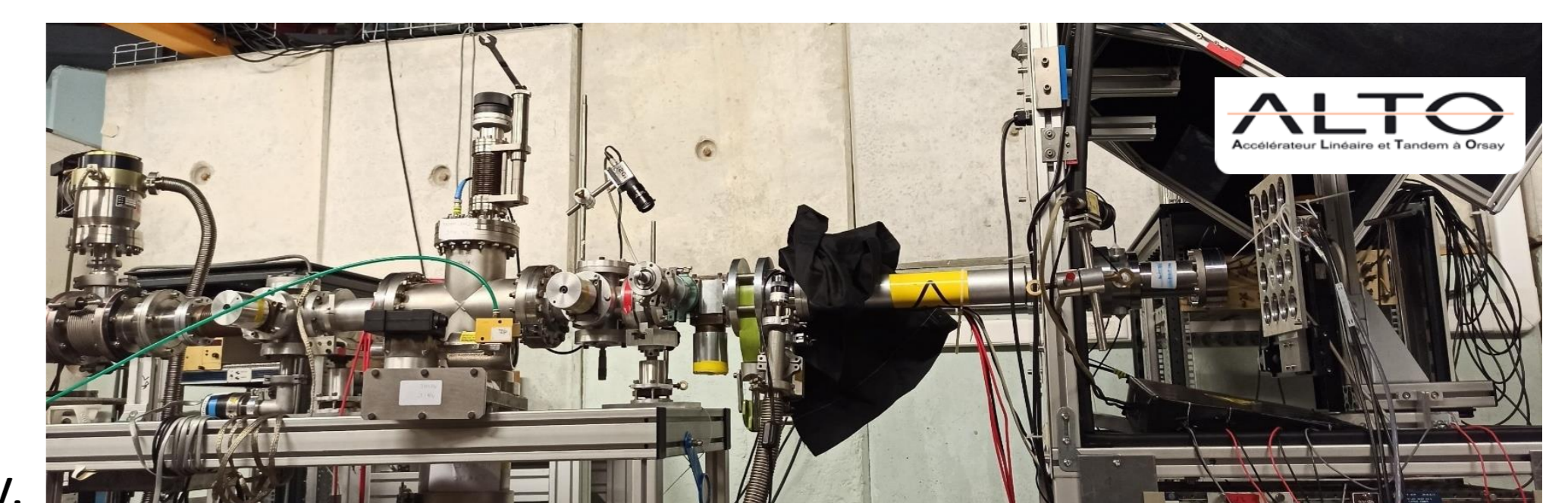


Figure 6

Radiograff beamline for *in vitro* irradiations with protons, He and Li ions at ALTO facility. The obtained data from irradiations at low energies will feed and enhance the NanOx model.

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